June 19, 2002. During this interview the pending rejections under 35 U.S.C. § 112, first and second paragraphs were discussed.

I. Status of the claims

After a restriction requirement, claims 1 and 3 are pending in this application. Claims 1 and 3 have been amended in order to more clearly define the subject matter of the invention in response to the Office's indefiniteness rejections. No claim was amended in order to overcome prior art. Furthermore, the scope of the claims was not narrowed by these amendments. No new matter has been added by these amendments.

II. General comments by the Office

The Office indicates that "the novelty of the invention regards the marker substrate [inhibiting] the enzyme." The Office further argues that inhibition of only the catalytic domain is not claimed and that the enzyme, the substrate, the marker substrate, and their interactions are known in the art.

In response to these comments, Applicant clarifies that the object of the invention is "to find substances which reduce or essentially prevent binding of substrates to the binding domain of a protein." Specification at p. 2, lines 5-6. That is, "in contrast to inhibitors according to the prior art, the substances of the invention do not inhibit the catalytic domain but rather interfere with binding of the substrate to the binding domain(s) of the enzyme." Specification at p. 6, lines 2-5.

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Various members of some families of enzymes, collagenases for example, share at least one catalytic domain even though the individual enzymes may have different biological functions. Therefore, inhibitors of the catalytic domain of a particular protein may also inhibit other proteins with a different function whose inhibition may not be desirable. Specification at p. 4, line 30 to p. 5, line 7. In this context, one utility of the invention lies in the fact that inhibition of the binding domain of a protein would allow a higher specificity of inhibition of a particular enzyme than inhibition of the catalytic domain would. *Id.*

The Office also inquires how the catalytic domain, without the binding domain, can be incubated with a substrate. Applicant prepared proteins containing only the catalytic domain without the binding domain by recombinant techniques. Specification at p. 3, lines 27-30.

III. Rejections under 35 U.S.C. § 112, first paragraph

The Office rejected claims 1 and 3 as containing subject matter that was not described in the specification in such a way as to allow one skilled in the art to make and/or use the invention. The Office argues that the "claims are directed to determining whether a substance is an inhibitor or a ligand and Table 1 is presented on page 11 of the specification." Office Action at p. 3, 2nd full ¶. The Office further argues that "no specific compounds and data obtained is shown to be correlated to the compounds being inhibitors only." *Id.* Applicant respectfully traverses this rejection.

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Results from carrying out the methods of the invention indicate whether a test substance binds to, and therefore is an inhibitor of, the binding domain of a protein. See *e.g.*, Examples 1, 2, and 3; p. 2, lines 5-6; p. 3, lines 9-11. An inhibitor of the binding domain of a protein is also an inhibitor of the catalytic activity of the protein with respect to a particular substrate if the substrate needs to bind to the binding domain of the protein before it is converted. In this case, the protein would not be able to chemically convert the substrate because the substrate would not be able to bind to the protein.

However, if a particular substrate does not need to bind to the binding domain of the protein before it is chemically converted, then an inhibitor of the binding domain of a protein would be considered a ligand and not an inhibitor with respect to that particular substrate. That is, the ligand will not inhibit conversion of the substrate.

Examples 3, 5, and 6 in Table 1 show inhibitors and/or ligands of the invention. Example 4 is included in Table 1 for comparison purposes as an example of an inhibitor of the catalytic domain of the protein that has been previously identified in the literature.

The Office also rejected claim 1 alleging that although the specification "is enabling for a single substrate-collagen, a single enzyme-collagenase, and a single marker substrate, [the specification] does not reasonably provide enablement for an[y] protein, any marker and any substrate." The Office argues that the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with the claims. The Office further argues that the "[q]uantity of experimentation

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necessary would be undue because of the large proportion of inoperative compounds claimed." Office Action at p. 4, 1st full ¶. Applicant respectfully traverses this rejection.

Applicant respectfully reminds the Office that the instant claims are drawn to methods to determine whether a substance is an inhibitor or a ligand of a protein. The instant claims do not claim compounds. Applicant reserves the right to address any arguments regarding the enablement of composition claims when and if necessary in future divisional applications.

The specification clearly conveys to the skilled artisan how to use the methods of the instant invention in general for any given protein that contains at least one catalytic domain and at least one binding domain. Specification at p. 2, lines 30-31; Examples 1-6. For instance, these inhibitors or ligands can be detected by comparing the transformation of the marker substrate in the presence of the test substance with the corresponding transformation occurring in appropriate control mixtures. One such control mixture contains the enzyme and the substrate marker but no substrate or test substance (*e.g.*, Example 1 in Table 1). "The transformation of the marker substrate in this control mixture indicate[s] the maximum conversion possible for the marker substrate because there [is] no inhibition of the catalytic domain." Example 1 at p. 12, lines 12-15.

Another control mixture contains the protein, the substrate marker, and the substrate but again, no test substance (*e.g.*, Example 2 in Table 1). "Transformation of the marker substrate in this second control mixture reflect[s] competitive inhibition of the

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catalytic domain by both the substrate and the marker substrate." Example 2 at p. 12, lines 19-21.

"If conversion of the marker substrate in the presence of a test substance is between the values obtained with these two control mixtures, an inhibitor or ligand of the protein has been found." Example 2 at p. 12, lines 23-25.

The method just described, coupled with the teachings of Examples 3, 5, and 6, can applied to the determination of whether a test substance is an inhibitor or a ligand of any protein that has at least one binding domain and at least one catalytic domain.

Additionally, the individual techniques involved in the methods of the invention, such as measuring conversion of a substrate for example, are routine experimentation in the art. The courts have recognized that such experimentation would not be undue because sufficient guidance is provided in the specification. *In re Wands*, 858 F.2d 731, 737; 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (indicating that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.") *See* also M.P.E.P. § 2164.01; 2164.01(a).

The Office further argues that the "[a]mount of direction or guidance presented is insufficient to predict which substances encompassed by the claims would work." Office Action at p. 4, 2nd full ¶.

As mentioned previously, the instant claims are drawn to methods, not compositions. Furthermore, there is no element of uncertainty in the claim that would

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require that the specification "predicts" which substance would be an inhibitor or ligand of the protein of interest. No predictive methods are claimed. The claimed method will simply determine whether the test substance is or is not an inhibitor or ligand of the protein of interest.

Therefore, in light of the teachings of the specification (*e.g.* Examples 1 and 2), which are applicable to any protein with at least one catalytic domain and at least one binding domain, the methods of the invention are clearly enabled in their full scope. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

IV. Rejections under 35 U.S.C. § 112, second paragraph

The Office also rejected claims 1 and 3 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter of the invention.

The Office argues that "[i]n claim 1(c), 'can bind' does not state what actually occurs." Applicant respectfully traverses this rejection. Applicant submits that the phrase in question is not indefinite when read in light of the specification. M.P.E.P. § 2173.02. However, with the sole purpose of expediting prosecution, Applicant has amended claim 1 by deleting the definitions of the components of the mixture used in the methods of the invention. These definitions can be found in the specification at p. 2, line 30 to p. 3, line 7. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

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The Office further argues that "claim 1 is directed to determining whether a test substance is an inhibitor or a ligand but lacks any correlating step to determine that." Office Action at p. 5, 1st full ¶. Applicant has amended claim 1 addressing the Office's concerns and respectfully requests that this rejection be withdrawn.

The Office also argues that claim 3, does not explain how the protein is used. Applicant respectfully traverses this rejection. Claim 3 is dependent from claim 1, and the word "used" was shorthand for "used in the method of claim 1." However, as the word "used" is superfluous in the claim, and with the sole purpose of expediting prosecution, Applicant has amended claim 3 addressing the Office's concerns. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Finally, the Office is requiring that the title of the application be changed to one that is more indicative of the invention to which the claims are directed.

With the sole purpose of expediting prosecution, Applicant has amended the title of the invention. Accordingly, Applicant respectfully requests that this requirement be withdrawn.

CONCLUSIONS

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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Should the Office determine that a telephone conference with Applicant's representatives would expedite prosecution, the Office is encouraged to contact the undersigned at (202) 408-4123.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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By: _____
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Date: July 1, 2002

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Appendix to Response and Amendment dated July 1, 2002

Amendment to the Title

A Method for Detecting **Protein Inhibitors and Ligands** ~~Active Ingredients~~ of Medical Value.

Amendments to the Claims

1. A method to determine whether a **test** substance ~~is an inhibitor~~**inhibits** or **acts as** a ligand of a protein, comprising:

incubating said **test** substance with a mixture, wherein said mixture comprises:

a) ~~a~~ **the** protein, ~~which contains at least one catalytic domain and at least one binding domain,~~

b) at least one marker substrate, ~~which binds to the catalytic domain and is converted by the protein,~~ and

c) at least one substrate~~, which can bind to the catalytic domain and to the binding domain~~; and

comparing the conversion of the marker substrate in the presence of the test substance with the corresponding conversion in control mixtures A and B, & test substance present?

wherein the control mixture A comprises the protein and the marker substrate; and the control mixture B comprises the protein, the substrate and the marker substrate same conditions?

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wherein the test substance is an inhibitor or ligand of the protein if the conversion of the marker substrate in the presence of the test substance is between the values obtained with control mixtures A and B.

3. The method as claimed in claim 1, wherein the protein ~~used~~ is collagenase, the substrate ~~used~~ is collagen, and the marker substrate ~~used~~ is (7-methoxycoumarin-4-yl)acetyl-Pro-Leu-Gly-Leu-(3-[2,4-dinitrophenyl]-L-2,3-diaminopropionyl)-Ala-Arg-NH_2.

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